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Bacteremia in patients with febrile neutropenia after chemotherapy at a university medical center in Malaysia

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Summary
Objectives: This study was initiated to determine the local profile of blood culture isolates and antibiotic sensitivities in febrile neutropenic patients following chemotherapy, and to establish if any modifications to treatment guidelines are necessary.
Design: A total of 116 episodes of febrile neutropenia admitted to the adult hematology ward at a university medical center in Malaysia were studied retrospectively from January 2004 to January 2005.
Results: The study showed 43.1% of febrile neutropenic episodes had established bacteremia. Gram-negative bacteria accounted for 60.3% of isolates. Sensitivities of Gram-negative bacteria to the antibiotics recommended in the Infectious Diseases Society of America (IDSA) guidelines were 86.1—97.2%. Coagulase-negative staphylococci were the most common Gram-positive organisms isolated (23.3%). The majority of these were methicillin-resistant.
Conclusions: Carbapenem monotherapy, as recommended in the 2002 IDSA guidelines, is effective treatment for the infections most often encountered at our center. Combination therapy with an aminoglycoside should be considered when using ceftazidime, cefepime or piperacillin—tazobactam, particularly in high-risk patients. Vancomycin should be used if a Gram-positive organism is suspected or isolated.

Introduction

In spite of new and exciting developments in recent years, cytotoxic chemotherapy remains the cornerstone of treatment in most hematological malignancies. The resulting

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neutropenia is a major cause of morbidity and mortality in these patients. Before the advent of the antibiotic era, mortality rates in neutropenic patients with leukemia and Gram-negative infections were as high as 91%.[1] The introduction of empirical antibiotic therapy dramatically altered the management of febrile neutropenia.[2,3] The mortality rate has fallen to as low as 7% as observed in the EORTC-IATG (European Organisation for Research and Treatment of Cancer-International Antimicrobial Therapy) therapeutic trials.[4]

Over the last three decades, there has been considerable change in the epidemiology of pathogens causing bacteremia in patients with febrile neutropenia. In the 1970s, Gram-negative infections caused 60—70% of bacteremia in neutropenic patients; in the 1990s, the majority of bacteremia was due to Gram-positive cocci.[5—8] This trend has been attributed to many factors: widespread use of quinolones as prophylaxis,[9,10] the use of long-term in-dwelling intravascular catheters,[11] increased incidence of severe mucositis as a result of increasingly potent chemotherapy, and the use of antacids and histamine blockers.

The fact that the epidemiology of pathogens is dynamic makes contemporary local data extremely important when making therapeutic decisions. Therapy in the adult hematology unit at University Malaya Medical Centre (UMMC) has been guided largely by external data and guidelines published by the Infectious Diseases Society of America (IDSA). The 2002 IDSA guidelines for the treatment of febrile neutropenia recommend initial therapy with ceftazidime, cefepime or a carbapenem as monotherapy, or combined with an aminoglycoside and/or vancomycin.[12] Hence, the aim of this study was to determine local patterns and antibiotic susceptibilities of the pathogens causing bacteremia in patients who have developed febrile neutropenia after chemotherapy.

Materials and methods

A retrospective study was conducted of all patients admitted with febrile neutropenia after chemotherapy to the adult hematology unit at UMMC between January 1, 2004 and January 31, 2005. Patients were included if they met all three of the following inclusion criteria: (1) fever, defined as a single oral temperature of 38.3 °C or an oral temperature of 38 °C lasting one hour; (2) neutropenia, defined as a neutrophil count of $<$500 cells/mm^3, or a count of $<$1000 cells/mm^3 with a predicted decrease to $<$500 cells/mm^3 within the next 48—72 hours; and (3) received chemotherapy prior to the episode of febrile neutropenia. Patients who had fever and neutropenia as a result of their underlying disease, without having received chemotherapy, were excluded. Each separate hospital admission for febrile neutropenia was defined as one episode. Subsequent hospital admissions for febrile neutropenia in the same patient were included as separate cases.

Bacteremia was defined as $\geq$1 blood culture yielding a pathogenic organism. If the isolate was a potential skin contaminant (such as coagulase-negative staphylococci, *Bacillus* or *Corynebacterium* species), all the following criteria needed to be met for it to be considered significant: the presence of an intravascular catheter, the initiation of antimicrobial therapy, and at least one of fever, temperature $<$36 °C, chills, or hypotension.[8] An infection was considered to be line-associated if there was clinical evidence of line infection, or if the criteria for bacteremia were satisfied in the absence of other sites of infection.

All available patient records were reviewed, and demographic data collected. Microbiological results were obtained from computerized laboratory records. The choice of empiric antibiotic regime by the treating physicians was guided by the IDSA guidelines.[12] Monotherapy with ceftazidime, cefepime or piperacillin—tazobactam was the usual first-line treatment, with conversion to a carbapenem by day 3 if the patient was deteriorating or still febrile. Vancomycin or antifungal therapy was added to the regime if indicated clinically or by microbiological findings. Antibiotic prophylaxis was given to 10 stem cell transplantation patients (norfloxacin and co-trimoxazole), two T cell lymphoblastic lymphoma/leukemia patients (co-trimoxazole as prophylaxis against *Pneumocystis jiroveci*), and one patient who did not require hospitalization during chemotherapy as decided by the attending physicians (amoxicillin—clavulanate and ciprofloxacin).

Antibiotic susceptibilities were assessed by disk diffusion using Clinical and Laboratory Standards Institute guidelines.[13] For isolates of *Escherichia coli* and *Klebsiella spp*, extended-spectrum β-lactamase (ESBL) production was screened for by testing ceftazidime and cefotaxime, and confirmed with the double-disk test.[14]

Results

A total of 120 admissions fulfilled the inclusion criteria. Of these, 116 were recruited into the study, and four were excluded due to missing records.

Patient profile

The median age of patients was 40 years (range 16—75 years). The ratio of males to females was almost 1:1. The majority of patients suffered from acute myeloid leukemia (51.7%) and non-Hodgkin's lymphoma (27.6%). Most (83.6%) of the patients had active disease, i.e., were either newly diagnosed, on treatment without having achieved remission, or relapsed. A total of 78 patients (67.2%) were receiving primary chemotherapy. Another ten patients (8.6%) had had hematopoietic stem cell transplantation. The remaining patients were receiving salvage chemotherapy. Three quarters of the patients were inpatients at the onset of fever. Seventy percent had an identifiable infective focus, the majority of which were line-related and respiratory infections. Co-morbidities were few, and included diabetes mellitus (11), chronic hepatitis B (6), hypertension (4), and HIV infection (2). Detailed patient characteristics are shown in Table 1.

Microbiology results

The 116 episodes of febrile neutropenia studied occurred in 67 patients. Of these, 50 episodes (43.1%) were blood culture positive, occurring in 37 patients. Of these, 35 episodes had bacteremia with a single pathogen, 10 episodes had two pathogens isolated, and in the remaining five episodes, three

Table 1 Patient characteristics ($N = 116$)

Patient characteristics	*n*	%
Race		
Chinese	79	68.1
Malay	26	22.4
Indian	9	7.8
Other	2	1.7
Underlying disease		
Acute lymphoblastic leukemia	16	13.8
Acute myeloid leukemia	60	51.7
Hodgkin's disease	3	2.6
Non-Hodgkin's lymphoma	32	27.6
Other	5	4.3
Disease status		
Remission	19	16.4
No remission	97	83.6
Treatment setting		
Primary chemotherapy	78	67.2
Salvage chemotherapy	28	24.1
Bone marrow transplantation	10	8.6
Presence of co-morbidities		
Yes	20	17.2
No	96	82.8
Duration of neutropenia		
>7 days	62	53
Hospitalization status		
Inpatient	86	74.1
Outpatient	30	25.9
Infective foci		
None	34	29.3
Lines	27	23.3
Respiratory	16	13.8
Perianal	8	6.9
Gastrointestinal	8	6.9
Mucositis	10	8.6
Abscess	6	5.2
Others	7	6.0
Use of antibiotic prophylaxis		
Yes	13	11.2
No	103	88.8

or more pathogens were isolated. The pathogens and their frequencies are shown in Table 2.

The majority, 44/73 (60.3%), were Gram-negative bacteria. *Enterobacteriaceae* were the most frequently isolated Gram-negative organisms, and coagulase-negative staphylococci (CoNS) were the Gram-positive organisms most frequently isolated. Gram-negative bacteremia was present in 35.5% of patients with acute leukemia, compared with only 8.6% of those with lymphomas ($p = 0.003$). The incidence of Gram-positive bacteremia in the leukemia group was 27.6% versus 14.3% in the lymphoma group ($p = 0.123$). Thirty-seven percent of patients with profound neutropenia, i.e., absolute neutrophil count <100 cells/mm^3, had Gram-negative bacteremia, compared with 19% of those with neutrophil counts >100 cells/mm^3 ($p = 0.03$).

Table 2 Pathogens isolated from 50 episodes of febrile neutropenia

Pathogen	*n*	% of total isolates
Gram-negative		
Escherichia coli	16	21.9
Klebsiella species	11	15.1
Enterobacter species	5	6.8
Pseudomonas aeruginosa	4	5.5
Acinetobacter baumannii	2	2.7
Proteus mirabilis	1	1.4
Stenotrophomonas maltophilia	1	1.4
Aeromonas hydrophila	1	1.4
Alcaligenes species	1	1.4
Pseudomonas species	1	1.4
Unidentified Gram-negative bacillus	1	1.4
Subtotal	44	60.3
Gram-positive		
Coagulase-negative *Staphylococcus*	17	23.3
Bacillus species	4	5.5
Staphylococcus aureus	2	2.7
Streptococcus species	2	2.7
Enterococcus species	2	2.7
Corynebacterium species	2	2.7
Subtotal	29	39.7
Total	73	100.0

Of the 13 patients taking antibiotic prophylaxis, five had bacteremic episodes, including four post-transplant patients on norfloxacin and co-trimoxazole, and one patient on amoxicillin–clavulanate and ciprofloxacin. One patient had *Enterococcus* bacteremia, while the other four had mixed Gram-positive and Gram-negative infections. Of the five Gram-negative isolates, comprising *E. coli* (3), *Pseudomonas aeruginosa* (1) and *Acinetobacter* species (1), all but the latter were resistant to the antibiotic prophylaxis used. The numbers involved are otherwise too small to draw conclusions about the impact of prophylaxis.

Line-related infections accounted for 23.3% of the total source of febrile neutropenia. Of the 12 line infections that were bacteremic, four (33.3%) yielded Gram-positive organisms, five (41.7%) yielded Gram-negative organisms, and three (25%) were mixed. Thus, line-related infections did not appear to predispose to Gram-positive bacteremia. None of the patients with mucositis in this series had Gram-positive bacteremia.

Local antimicrobial sensitivity patterns

Details of the in vitro sensitivity profiles of the four most frequently isolated Gram-negative pathogens (*E. coli*, *Klebsiella spp*, *Enterobacter spp*, and *P. aeruginosa*) are shown in Table 3. These four pathogens accounted for 81.8% (36/44) of all Gram-negative isolates. Susceptibility rates were highest for carbapenems (94.4%), and the aminoglycosides amikacin (97.2%) and netilmicin (94.4%).

A total of 4/44 (9.1%) of Gram-negative isolates were resistant to imipenem and meropenem, including one strain

Table 3 Antibiotic susceptibilities of the most frequently isolated Gram-negative organisms (*Escherichia coli*, *Klebsiella* species, *Enterobacter* species and *Pseudomonas aeruginosa*)

Antibiotic	No. susceptible (%)				
	E. coli (*n* = 16)	*Klebsiella spp* (*n* = 11)	*Enterobacter spp* (*n* = 5)	*P. aeruginosa* (*n* = 4)	Total (*n* = 36)
Amoxicillin–clavulanate	9 (56.3%)	9 (81.8%)	1 (20%)	0	19 (52.8%)
Cefepime	14 (87.5%)	10 (90.9%)	4 (80%)	3 (75%)	31 (86.1%)
Ceftazidime	14 (87.5%)	10 (90.9%)	4 (80%)	3 (75%)	31 (86.1%)
Imipenem	16 (100%)	11 (100%)	4 (80%)	3 (75%)	34 (94.4%)
Meropenem	16 (100%)	11 (100%)	4 (80%)	3 (75%)	34 (94.4%)
Piperacillin–tazobactam	16 (100%)	9 (81.8%)	4 (80%)	3 (75%)	32 (88.9%)
Ciprofloxacin	6 (37.5%)	9 (81.8%)	5 (100%)	4 (100%)	24 (66.7%)
Amikacin	15 (93.8%)	11 (100%)	5 (100%)	4 (100%)	35 (97.2%)
Gentamicin	12 (75%)	11 (100%)	5 (100%)	4 (100%)	32 (88.9%)
Netilmicin	14 (87.5%)	11 (100%)	5 (100%)	4 (100%)	34 (94.4%)

each of *Stenotrophomonas maltophilia*, *Aeromonas hydrophila*, *P. aeruginosa*, and *Enterobacter spp*. Of 27 *E. coli* and *Klebsiella spp*, three (11.1%) were ESBL-producers. The total ceftazidime and cefepime sensitivity rate for the four main Gram-negative pathogens was 86.1%.

All Gram-positive isolates were sensitive to vancomycin. Of the 17 CoNS isolated, 76% were methicillin-resistant. Both the isolates of *Staphylococcus aureus* were methicillin-sensitive.

Discussion

In order to effectively treat infections in the neutropenic patient with fever, knowledge of the likely pathogens and the local antibiotic sensitivity patterns in individual centers is crucial. The etiology of bacteremia in febrile neutropenic patients after being given chemotherapy in this study was predominantly Gram-negative (60.3%), with *E. coli*, *Klebsiella spp*, *Enterobacter spp* and *P. aeruginosa* the most frequently isolated organisms. Similar results have been found in some European centers, which have reported the reemergence of Gram-negative bacilli as predominant pathogens; this may partly be due to decreased use of quinolone prophylaxis.[7] Apart from stem cell transplantation patients and *Pneumocystis* prophylaxis in patients with T cell lymphoblastic lymphoma/leukemia, prophylaxis is not routinely used in our center. Therefore, the initial choice of empirical therapy at our center must have adequate Gram-negative and anti-pseudomonal coverage. Our susceptibility results suggest that monotherapy with a carbapenem is a viable treatment strategy. When using ceftazidime, cefepime or piperacillin–tazobactam, the addition of an aminoglycoside, preferably amikacin, is advisable. Concern regarding renal toxicity should not prohibit the use of these agents as our patient population is young, with few co-morbidities, and 99% had a baseline serum creatinine of <180 μmol/l.

Surveillance is also important for the monitoring of rates of resistant organisms, such as ESBL-producers and carbapenem-resistant *Enterobacteriaceae*. Although the latter are still relatively rare,[15] the isolation of a carbapenem-resistant *Enterobacter* from the bloodstream of one patient is of great concern. Similarly, our 11.1% rate of ESBL-producers amongst *E. coli* and *Klebsiella spp* is worrying, as others have reported an increasing incidence of serious infections caused by ESBL-producers.[7,16]

The Gram-positive pathogens most commonly isolated were CoNS with a high rate of methicillin resistance (76%), consistent with previous data.[8] The numbers of *S. aureus* and *Streptococcus spp* infections in this study were small, with only two isolates each, thus any comment on the sensitivity patterns of these organisms would be invalid. Vancomycin should still be the empirical treatment of choice when a Gram-positive pathogen is suspected clinically, or cultured. Therapy should be reviewed once cultures are available.

The significantly higher rates of bacteremia in the acute leukemia group compared to the lymphoma group in this study, is also not surprising. This is likely due to the more myelosuppressive chemotherapy, which usually results in a longer duration of neutropenia, a known risk factor for developing infections.[17] Profound neutropenia is also a risk factor for developing infection and again this has been demonstrated in many studies.

This study only looked at those patients who had developed febrile neutropenia after chemotherapy, to determine more accurately the possible infections in our hospital rather than those infections from the community. This may not represent the reality of all patients who have febrile neutropenia, especially patients who are newly diagnosed with acute leukemia. It is important to realize the limitations of this study.

In patients who have febrile neutropenia after chemotherapy, it is important for the attending clinicians to risk-stratify the patients in order to prevent any fatal complications from infection. Further study and extrapolation of the local data will be helpful for risk stratification-based management.

Conflict of interest: No conflict of interest to declare.

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